Transdermic systems containing 2 active ingredients in separate compartments, their preparation process and their use as medicaments.

The present invention relates to a new device intended for the administration by transdermic route of an active ingredient combined with another active ingredient and their preparation process.

The Applicant has studied a new galenic form:
which allows an active ingredient (I) and an active ingredient (II) to be combined in a single entity, being able to be administered simultaneously, separately and over a period of time to prevent or treat an illness requiring a bitherapy,
- which resolves problems of differences in stability of active ingredients in polymers used for loaded layers,
- which allows the administration of each active ingredient under optimum conditions in order to obtain a pharmaceutically acceptable transcutaneous flow and avoids all interaction between a compound and the matrix of the other compound,
- which conforms with the stipulated requirements regarding doses and the day of administration of each active ingredient (predosage), while avoiding the purchase, and the manipulation of two individual patches.

In the context of an oestrogen-progestogen combination, the last point is particularly important for hormone replacement treatment relating to the menopause and especially the prevention or the treatment of osteoporosis as well as for contraceptive treatment.

To the knowledge of the Applicant, no galenic form used to deliver two active ingredients simultaneously, separately and over a period of time is available in the form that is proposed in this Patent Application.

According to the state of the art, active ingredients are:
- either in two separate patches,
- or mixed in the same matrix,

- or in superposed matrices,
- or in adjacent matrices on the same protective film.

When active ingredients are in two separate patches, the prescription requiring simultaneous application of the two patches may not be scrupulously adhered to, while if the patient finds these two patches in a single unit, he will apply them simultaneously: all risk of omission is thus avoided. This also facilitates the simultaneous changing of the two patches during lengthy treatment necessitating the renewal of patches. This thus avoids all risk of over- or under-dosage of one of the active ingredients as opposed to the other.

When the compounds are mixed in the same matrix, problems of stability can appear. Moreover, there can also be interaction or competition problems which modify the flow of one of the active ingredients in favour of the other.

When each of the components is located in superposed matrices, the problems raised previously can equally appear.

When matrices are adjacent, there can be migration or distribution problems from one matrix to the other which also risks alteration to the flow and/or the stability of one of the active ingredients in favour of the other.

Therefore a subject of the invention is a device (cf. Figure 1) intended for the transdermic administration of an active ingredient (I) and an active ingredient (II), comprising two compartments (A) and (B),

- compartment (A) containing an adhesive polymer matrix loaded with active ingredient (I), to which one or more additives can optionally be added,
- and compartment (B) containing an adhesive polymer matrix loaded with active ingredient (II), to which one or more additives can optionally be added, each matrix being respectively covered with a protective film (a) and (a') which is identical or different, characterised in that compartment (A) is separated from compartment (B) by an empty space of between 1 and 10 mm and characterised in that compartments (A) and (B) are supported by the same peel-off protective film (b).

To each polymer matrix containing the active ingredient, it is possible to add a hydrophilic additive and/or absorbent promoter and/or plasticizer and/or any other additive known to a man skilled in the art which might improve flow, adhesion and transdermic system stability criteria.

According to the invention, compartment (A) has a surface area of between 5 and 50 cm^2 and compartment (B) has a surface area of between 5 and 50 cm^2.

The surface of each matrix (A) and (B) can be different in order to more readily distinguish between the two patches, or for reasons of required doses.

The devices as previously described can be of any shape. Each compartment (A) or (B) can also be of any shape including round, oval, rectangular or square.

The peel-off protective film (b) is characterised in that it supports two separate compartments (A) and (B) respectively containing active ingredient (I) and active ingredient (II).

Once this peel-off protective film has been removed, two separate patches are obtained which are applied to the skin or mucous membranes so that administration of active ingredient (I) and active ingredient (II) is simultaneous, separate or spread over a period of time.

According to the invention, there can also be one or more fixing means between the two compartments (A) and (B) in order to obtain the connection of the two patches once the peel-off protective film (b) is removed.

The "bipatch" which is a subject of the invention also allows the administration of any combination of medicaments known to a man skilled in the art in order to provide bitherapy.

The invention also extends to "bipatches" allowing not only the administration of combinations having a synergistic or compensatory effect for a single therapeutic purpose, but also the juxtaposition of active ingredients each of which having a separate therapeutic role.

This "bipatch" which is a subject of the invention thus simply resolves the various problems encountered in mixed

patches of the prior art, and presents an appropriate response to the objectives described previously. It also offers the following advantages: by applying two separate matrices on the same peel-off protective film, it is easy to:

- separately optimise the formulations containing the active ingredients (selection of the support polymer, selection of an absorption promoter, selection of the hydrophilic polymer, selection of a plasticizer, optimisation of grammage), as a function of the required ashesion and flow criteria,
- separately optimise the concentrations of the active ingredients as a function of required stability and transcutaneous flow criteria and prescribed doses,
- obtain compartments of identical or different sizes, by a simple manufacturing process.

Peel-off protective film (b)

The peel-off protective films used are films intended to protect the adhesive side to be stuck on the skin from the transdermic system after manufacture and during storage.

Among the peel-off protective films known to a man skilled in the art, the preferred choice is a polyester film such as Scotchpak® 1022 (3M Health Care Limited), one side of which is treated with fluorocarbons, or a transparent polyester film Silox® B5Y/O (Akrosil™), to one side of which an anti-adhesive treatment has been applied using Dow-Corning's Bio-release silicones.

Adhesive polymer matrix

Adhesive polymer matrices containing an active ingredient are selected from a certain number of polymers which are available commercially and/or known to a man skilled in the art. These are in particular polymers or copolymers comprising a network of polyisobutylene or polyacrylic chains, ethylene and vinyl acetate (EVA) copolymers or silicone polymers. If appropriate any additive known to a man skilled in the art of transdermic systems can be added to these polymers.

This matrix can be mono- or multi-layered. Compartments A and B can also contain a reservoir system.

Among the polyisobutylene chains used there can be

mentioned those marketed under the mark Vistanex® (EXXON) or Oppanol® (BASF).

Among the acrylic polymers there can be mentioned:

- the acrylic polymers Gelva® 737 and 788 comprising a mixture of 2-ethylhexyl acrylate and vinyl acetate,
- the Acronal® acrylic polymers and in particular Acronal® V205 and DS 3405,
- the Durotak® self-crosslinkable acrylic solutions and in particular Durotak® 126-1753, 280-2516, 380-1054,
- the Eudragit® acrylic and methacrylic ester copolymers and in particular Eudragit® RL100 and S100,
- the aqueous dispersion of neutral methacrylates Eudragit® NE 30D.

Among the silicone polymers there can be mentioned those with strong instant adhesive power (BIO PSA®_7-4301), and those with medium instant adhesive power (BIO PSA® 7-3045, 7-4201 or 7-4202). (Dow Corning Health Care Centre Europe).

Adhesive power is characterised by peeling force and adhesion force: this adhesive force increases on passing from "low tack" grade to "medium tack" and then to "high tack". The parameter used to modulate this physical characteristic is the silicone polymer/resin ratio.

By medium adhesive power is meant a ratio of 40/60. By strong adhesive power is meant a ratio of 45/55.

Absorption promoters

The absorption promoters which are optionally used are selected from a certain number of promoters which are commercially available and/or known to a man skilled in the art, and in particular diethyleneglycol monoalkyl ethers, saturated polyglycolized glycerides comprising glycerides and polyethyleneglycol esters of fatty acids containing from 6 to 14 carbon atoms, monoalkylates containing 8 to 12 carbon atoms, 1,2 propane-diol and ethanol, or a combination of these components.

Hydrophilic additives

- The hydrophilic additives which are optionally used are selected from a certain number of polymers which are commercially available and/or known to a man skilled in the

art including guar gums, xanthane gum and polyvinyl-pyrrolidone.

Plasticizers

The purpose of any plasticizers which are optionally used is to improve the instant adhesion process. In particular, these are silicone fluid or cetiol S (dioctyl cyclohexane) or glycerol triacetate.

Empty space

The empty space used to separate the two compartments (A) and (B) can be from 1 to 10 mm. The preferred size is from 2 to 4 mm.

Protective films (a) and (a')

The protective films used are supports on which the different layers constituting the patch are applied, in order to obtain an indissociable system. One of the products from 3M's Scotchpak® range is preferably used, and more particularly Scotchpak® 1109, a film which is skin-coloured, occlusive and flexible, or Scotchpak® 1006, or a product from Hoechst's Hostaphan® range, and more particularly the RN range (RN23, RN50 or RN75). Of course, the matrices can be covered using identical or different protective films.

More particularly, a subject of the invention is a device intended for the transdermic administration as described previously, characterised in that compartment (A) contains a progestomimetic compound and compartment (B) contains an oestrogen compound.

More specifically, a subject of the invention is devices as described previously, characterised in that the progestomimetic is selected from the following components: norethindrone (17α)-17-hydroxy-19-norpregn-4-en-20-yne-3-one, norgestimate (17α)-17-(acetyloxy)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one-3-oxyme, norgesterone (17α)-17-hydroxy-19-norpregna-5(10),20-dien-3-one, Trimegestone 17alpha-methyl-17beta-(2-hydroxy-1-oxo-propyl)-estra-4,9-dien-3-one (21S), promegestone (17β)-17-methyl-17-(1-oxopropyl)estra-4,9-dien-3-one, Levonorgestrel Form (-) of 13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one (norgestrel), ST 1435 16-methylene-17α-acetoxy-19-nor-4-pregnene-3,20-dione,

Medroxyprogesterone (6α)-17-hydroxy-6-methylpregn-4-ene-3,20-dione, Gestodene (17α)-13-ethyl-17-hydroxy-18,19-dinorpregna-4,15-dien-20-yn-3-one, Dienogest 17-hydroxy-3-oxo-19-nor-17α-pregna-4,9-diene-21-nitrile, Desogestrel (17α)-13-ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-17-ol, Ketodesogestrel (17α)-13-ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-3-one-17-ol, Norethisterone acetate (17α)-17-acetoxy-19-norpregn-4-en-20-yn-3-one, Demegestone 17-methyl-19-norpregna-4,9-diene-3,20-dione and combinations of these compounds.

More specifically, a subject of the invention is devices as described previously, characterised in that the progestomimetic compound is Trimegestone.

Trimegestone (17alpha-methyl-17beta-(2hydroxy-1-oxo-propyl)-estra-4,9-dien-3-one(21S)) is a powerful progestomimetic described in European Patent EP-0007823.

More specifically, a subject of the invention is devices as described previously, characterised in that the oestrogen compound is selected from the following compounds: 17-beta-oestradiol, ethynyl oestradiol, oestrone and oestrogen of "equine origin" such as Premarin® and combinations of these compounds.

More specifically, a subject of the invention is devices as described previously, characterised in that the oestrogen compound is oestradiol.

When the oestrogen compound is oestradiol, the loaded matrix will preferably be a mono-layer matrix comprising a 2-ethylhexyl acrylate and vinyl acetate copolymer, to which a hydrophilic polymer may optionally be added. More specifically, this will be the Gelva® 737 copolymer containing 72% of 2-ethylhexyacrylate and 28% of vinylacetate.

The preferred hydrophilic polymer is polyvinyl-pyrrolidone. More specifically, this will be Kollidon® 30 or 90F.

The quantity of oestradiol incorporated in a polymer matrix as defined previously is between 1% w/w and 10% w/w. This percentage corresponds to the dry weight of the coated

mass after evaporation of the solvent.

When the progestomimetic compound is Trimegestone, the loaded matrix will preferably be,

- either a mono-layer matrix comprising a silicone polymer to which a plasticizer such as silicone fluid is optionally added,
- or a two-layer matrix,

a) the first layer comprising a silicone polymer loaded with Trimegestone, and

b) the second layer, the layer that adheres to the skin, comprising a silicone polymer.

In any event, the matrices are preferably constituted by a polydimethylsiloxane chain network having a strong adhesive power such as BIO PSA® 7-4301.

The quantity of Trimegestone incorporated in a polymer matrix as defined previously is between 1% w/w and 10% w/w. This percentage corresponds to the dry weight of the coated mass after evaporation of the solvent.

As Trimegestone (17alpha-methyl-17beta-(2-hydroxyl-oxo-propyl)-estra-4,9-dien-3-one(21S)) is not stable in the matrix used for the oestradiol, the device which is a subject of the invention is particularly appropriate for the administration of Trimegestone combined with oestradiol.

More specifically, a subject of the invention is devices as described previously, presenting the following characteristics:

BIPATCH 1 comprising

- a peel-off protective film (b) supporting two compartments (A) and (B), separated by an empty space of 1 to 10 mm,
- compartment (A) containing a mono-layer matrix, covered by a protective film (a), and constituted by a silicone polymer loaded with Trimegestone, and optionally a plasticizer,
- and compartment (B) containing a mono-layer matrix, covered with a protective film (a'), constituted by a 2-ethylhexyl acrylate and vinyl acetate copolymer, loaded with oestradiol and optionally a hydrophilic polymer.

BIPATCH 2 comprising

- a peel-off protective film (b) supporting two compartments

(A) and (B), separated by an empty space of 1 to 10 mm,
- compartment (A) containing a two-layer matrix covered by a protective film (a),
a) the first layer being constituted by a silicone polymer with a strong adhesive power loaded with Trimegestone,
b) the second layer, the layer that adheres to the skin, also being constituted by a silicone polymer.
- and compartment (B) containing a mono-layer matrix, covered with a protective film (a'), constituted by a 2-ethylhexyl acrylate and vinyl acetate copolymer, loaded with oestradiol and optionally a hydrophilic polymer.

More specifically, a subject of the invention is devices as described previously, containing:

BIPATCH 1a comprising
- a peel-off protective film (b) supporting two compartments (A) and (B), separated by an empty space of 1 to 10 mm,
- compartment (A) containing a mono-layer matrix, covered by an opaque protective film (a) and constituted by 80 to 99% w/w of silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone and 0 to 10% w/w of silicone fluid or Cetiol® S,
- compartment (B), containing a mono-layer matrix covered by a protective film (a') and constituted by 60 to 99% w/w of Gelva® 737 loaded with 1 to 10% w/w of oestradiol and 0 to 30% w/w of Kollidon®.

BIPATCH 2a comprising
- a peel-off protective film (b) supporting two compartments (A) and (B), separated by an empty space of 1 to 10 mm,
- compartment (A) containing a two-layer matrix covered by a protective film (a),
a) the first layer being constituted by 90 to 99% w/w of a silicone polymer having a strong adhesive power loaded with 1 to 10% w/w of Trimegestone,
b) the second layer, the layer that adheres to the skin, also being constituted by a silicone polymer with a strong adhesive power,
- compartment (B), containing a mono-layer matrix covered by a protective film (a') and constituted by 60 to 99% w/w of

Gelva® 737 loaded with 1 to 10% w/w of oestradiol and 0 to 30% w/w of Kollidon®.

According to the invention, the transcutaneous flow of oestradiol is between 0.1 and 2.5 $\mu g.cm^{-2}.h^{-1}$ and the transcutaneous flow of Trimegestone is between 0.1 and 3 $\mu g.cm^{-2}.h^{-1}$.

A subject of the invention is also the manufacture of devices as described previously.

The production technique for transdermic systems which are a subject of the invention is coating. The general principle is as follows:

Stage I: for the manufacture of the patch corresponding to compartment (A)

1 - the silicone adhesive polymer layer loaded with active ingredient (I) and optionally one or more additives such as a hydrophilic polymer, an absorption promoter or a plasticizer is coated on the protective film (a),

2 - the solvent is evaporated until the "matrix loaded with active ingredient (I)/protective film (a)" set corresponding to compartment (A) is obtained,

3 - the "matrix loaded with active ingredient (I)/protective film (a)" set is colaminated on the peel-off protective film (b'),

4 - a patch of 5 to 50 cm^2 is cut out.

Stage II: for the manufacture of the patch corresponding to compartment (B)

1 - the adhesive polymer layer loaded with active ingredient (II) and optionally one or more additives such as a hydrophilic polymer, an absorption promoter or a plasticizer is coated on the protective film (a'),

2 - the solvent is evaporated until the "matrix loaded with active ingredient (II)/protective film (a')" set corresponding to compartment (B) is obtained,

3 - the "matrix loaded with active ingredient (II)/protective film (a')" set is colaminated on the peel-off protective film (b''),

4 - a patch of 5 to 50 cm^2 is cut out.

Stage III: for the manufacture of the "bipatch"

1 - the peel-off protective film (b') is peeled from the patch obtained in Stage I,

2 - the "matrix loaded with active ingredient (I)/protective film (a)" set is transferred to the peel-off protective film (b),

3 - the peel-off protective film (b') is peeled from the patch obtained in Stage II,

4 - the "matrix loaded with active ingredient (II)/protective film (a')" set is transferred to the previous peel-off protective film (b), respecting a distance of 1 to 10 mm between compartments (A) and (B).

In this way the "bipatch" is obtained characterised in that it contains (see Figure 1):

- a peel-off protective film (b),
- a compartment (A) constituted by a matrix loaded with active ingredient (I) and covered by a protective film (a)
- a compartment (B) constituted by a matrix loaded with active ingredient (II) and covered by a protective film (a'), the two compartments being separated by an empty space of 1 to 10 mm.

In combination with an oestrogen, the progestative Trimegestone exhibits a strong antioestrogenic effect on the uterus without showing any antioestrogenic effect on the bone structure.

The Trimegestone/oestradiol combination as described in this Application can thus be used simultaneously, separately or over a period of time for hormone replacement treatment for the menopause and the prevention or treatment of osteoporosis. It allows the prevention of the symptoms and consequences of the menopause such as hot flushes, sweating, vaginal atrophy and dryness, urinary symptoms and in the long term a reduction in the bone structure mass with an increased risk of fracture and the loss of the cardio-vascular protection provided by oestrogens.

The oestro/progestative combination described in this Application can also be used as a contraceptive.

Finally, the subject of this invention is therefore a device as described previously for use in a process for

delivering several medicaments by application of the two matrices of the device to the said patient's skin or mucous membranes.

Examples of treatment using the bipatch

The examples of treatment below illustrate the invention without however limiting it. For each bipatch, adhesion lasts from 4 to 7 days.

1. Trimegestone combined with oestradiol

In the context of hormone replacement treatment for the menopause and in particular in the prevention or treatment of osteoporosis.

1.1 Sequential administration of Trimegestone and continuous administration of oestradiol:

Treatment a

Continuous administration of the oestradiol (28-day cycles with no break between cycles) at a dose of 25 to 200 μg per day and of Trimegestone for the last 14 days of each 28-day cycle at a dose of 0.05 to 2.5 mg per day. The trimegestone/oestradiol bipatch according to the invention is therefore used for the last 14 days (i.e. 2 to 4 bipatches).

Treatment b

Administration of oestradiol 28 days per month at a dose of 25 to 200 μg per day and of the Trimegestone for the last 14 days of the administration of oestradiol, at a dose of 0.05 to 2.5 mg per day. The treatment is stopped for 3 days per month at the end of each 28-day cycle. The trimegestone/oestradiol bipatch according to the invention is therefore used for the last 14 days (i.e. 2 to 4 bipatches).

Treatment c

Administration of the oestradiol 28 days per month at a dose of 25 to 200 μg per day and of the Trimegestone patch for the first 14 days of the administration of oestradiol, at a dose of 0.05 to 2.5 mg per day. The treatment is administered either without a break between each 28-day cycle or with a break of 2 to 3 days per month at the end of each cycle. The trimegestone/oestradiol bipatch according to the invention is therefore used for the last 14 days (i.e. 2 to 4 bipatches).

Treatment d

Administration of the oestradiol 25 days per month at a dose of 25 to 200 μg per day and of the Trimegestone at a dose of 0.05 to 2.5 mg per day for the last 11 to 14 days of administration of the oestradiol. The treatment is stopped for 5 to 6 days per month at the end of the 25-day cycle.

The trimegestone/oestradiol bipatch according to the invention is therefore used for the last 11 to 14 days (i.e. 2 to 4 bipatches).

1.2 Continuous administration of Trimegestone and oestradiol

Continuous transdermic administration of oestradiol at a dose of 25 to 200 μg per day and of Trimegestone at a dose of 0.05 to 2.5 mg per day. There is no break in treatment. The trimegestone/oestradiol bipatch according to the invention is therefore used for the 28 days (i.e. 4 to 8 bipatches).

2) Trimegestone combined with ethynyloestradiol

In the context of use as a contraceptive.

Trimegestone is continuously administered by transdermic route in combination with ethynyloestradiol for 21 to 28 days per cycle. This treatment therefore requires the successive application of 3 to 8 Trimegestone/ethynyloestradiol bipatches.

Examples of bipatches according to the invention are shown hereafter in the experimental section. The following examples illustrate the invention without however limiting it.

Example 1:

Patch containing Trimegestone combined with oestradiol

BIPATCH 1b

This bipatch has the following characteristics:

- a Scotchpak® 1022 peel-off protective film supporting two compartments (A) and (B), each separated by a gap of 2 to 4 mm
- compartment (A) contains a mono-layer matrix, covered by a Scotchpak® 1006 opaque protective film and constituted by 96% w/w of silicone polymer with a strong instant adhesive power loaded with 3% w/w of Trimegestone and 1% of silicone fluid (7-9120, 12000 cSt). The grammage is equal to 60 g/m².

- and compartment (B) contains a mono-layer matrix, covered by a Scotchpak® 1109 or Hostaphan® RN23 protective film and constituted by 73% w/w of a Gelva® 737 layer loaded with 2% w/w of oestradiol and 25% of Kollidon® 90F.
The grammage is equal to 80 g/m².

BIPATCH 2b

This bipatch has the following characteristics:
- a Scotchpak® 1022 peel-off protective film supporting two compartments (A) and (B), each separated by a gap of 2 to 4 mm
- compartment (A) contains a two-layer matrix covered by a Scotchpak® 1006 protective film,
a) the first layer of 60 g/m² grammage, loaded with 3% w/w of Trimegestone, constituted by 97% w/w of silicone polymer with a strong instant adhesive power,
b) the second layer, the layer which adheres to the skin, constituted by a silicone polymer with a strong adhesive power; its grammage is equal to 30 g/m².
The total grammage is thus equal to 90 g/m².
- and compartment (B) containing a mono-layer matrix, covered by a Scotchpak® 1109 or Hostaphan RN23 protective film and constituted by 73% w/w of a Gelva® 737 layer loaded with 2% w/w of oestradiol and 25% w/w of Kollidon® 90F. The grammage is thus equal to 80 g/m².

Example 2: Quantity of active ingredient in each compartment

The quantity x of active ingredient can be expressed by the following general formula
where
G, expressed in mg/cm² expresses the total grammage of the coated mass (sum of the grammages of each coated layer in the case of a multi-layer patch)
S is the surface area of the patch expressed in cm²
p is the percentage of active ingredient in the set of coated mass, expressed in % w/w,
then the coated mass, called M, calculated by M=G. S is expressed in mg/patch.
Thus x = p.M/100 = p.G.S/100 expressed in mg/patch

	compartment (A)	compartment (B)
G (mg/cm^2)	6	8
p (%)	3	2
min. S (cm^2)	5	5
max. S (cm^2)	50	50
min. x (mg/patch)	0.9	0.8
max. x (mg/patch)	9	8

Figure No.1:

(B) Compartment containing active ingredient (II)
(A) Compartment containing active ingredient (I)
(a) Protective film
(a') Protective film
(b) Peel-off protective film